

**What is claimed is:**

1. A method of identifying associated cell signaling proteins, the method comprising:
  - 5 a) producing and storing a comparison value for each pair of said cell signaling proteins in response to data values representing physical properties of respective cell signaling proteins; and
  - b) identifying cell signaling protein pairs having comparison values satisfying a condition indicative of an association between the cell signaling proteins.
- 10 2. The method of claim 1 wherein producing and storing comprises producing and storing in a random access memory, said comparison value.
3. The method of claim 1 further comprising normalizing said data values relative to at least one reference value, prior to producing said comparison values.  
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4. The method of claim 1 wherein identifying comprises producing a list of pairs of associated cell signaling proteins.
5. The method of claim 1 wherein identifying comprises producing a list of clusters of associated cell signaling proteins.
- 20 6. The method of claim 4 wherein identifying further comprises identifying a cluster of associated cell signaling proteins, said cluster comprising a group of said pairs of associated cell signaling proteins for which each member of each said pair is present in at least one other pair of said group.

7. The method of claim 5 wherein identifying each said cluster comprises:

- a) generating a cluster list associated with a first cell signaling protein pair, said cluster list comprising an identification of said first cell signaling protein pair;
- 5 b) adding, to said cluster list, an identification of each of said pairs that includes at least one cell signaling protein already present in said cluster list;
- c) repeating said adding following each said adding of pairs to said cluster list, to effectively add to said cluster list each of said pairs that includes at least one cell signaling protein present in at least  
10 one pair added to said cluster list;
- d) eliminating, from said cluster list, each of said pairs that includes at least one cell signaling protein not found in at least one other pair in said cluster list; and
- 15 e) repeating said eliminating following each said eliminating of pairs, to effectively eliminate from said cluster list each of said pairs that includes at least one cell signaling protein not present in at least one other non-eliminated pair in said cluster list.

8. The method of claim 1 further comprising receiving sets of cell  
20 signaling protein data, each set comprising said data values, said data values representing amounts of respective corresponding cell signaling proteins in biological material corresponding to said set.

9. The method of claim 8 wherein producing said comparison values  
25 comprises producing a coexpression coefficient for each pair of said cell signaling proteins, each said coexpression coefficient representing a degree of coexpression of one cell signaling protein of said pair and the other cell signaling protein of said pair.

10. The method of claim 9 wherein producing each said coexpression coefficient comprises:
  - a) for each set, calculating a difference value equal to an absolute value of a difference between said data value corresponding to said one cell signaling protein and said data value corresponding to said other cell signaling protein; and
  - b) adding said difference values for each of said sets to produce a sum of difference values.
11. The method of claim 10 wherein producing each said coexpression coefficient further comprises dividing said sum by the number of said sets to produce said coexpression coefficient corresponding to said one cell signaling protein and said other cell signaling protein.
12. The method of claim 10 wherein identifying cell signaling protein pairs comprises identifying each cell signaling protein pair having a coexpression coefficient less than or equal to a threshold coexpression value.
13. The method of claim 10 wherein identifying cell signaling protein pairs comprises producing a list of coexpressed cell signaling protein pairs, said list comprising an identification of each said cell signaling protein pair having a coexpression coefficient less than or equal to said threshold coexpression value.
14. The method of claim 13 wherein identifying cell signaling protein pairs further comprises producing a list of clusters of coexpressed cell signaling protein pairs, each said cluster comprising a group of said coexpressed cell signaling protein pairs for which each member of each pair is present in at least one other pair of said group.
15. The method of claim 1 further comprising receiving sets of cell signaling protein data, each set comprising said data values, said data

values indicating phosphorylation states of respective cell signaling proteins in biological material corresponding to said set.

16. The method of claim 15 wherein producing said comparison values comprises producing a coregulation coefficient for each pair of said cell signaling proteins, each said coregulation coefficient representing a degree of coregulation of one cell signaling protein of said pair and the other cell signaling protein of said pair.
17. The method of claim 16 wherein producing each said coregulation coefficient comprises:
- a) for each set, assigning a pair state value as a function of phosphorylation states of said one cell signaling protein and said other cell signaling protein; and
  - b) adding said pair state values for each of said sets to produce a sum of pair state values.
18. The method of claim 17 wherein producing each said coregulation coefficient further comprises dividing said sum by the number of said sets to produce said coregulation coefficient corresponding to said one cell signaling protein and said other cell signaling protein.
19. The method of claim 17 wherein assigning a pair state value comprises:
- a) assigning a first pair state value when said one cell signaling protein and said other cell signaling protein are both in a phosphorylated state;
  - b) assigning a second pair state value when said one cell signaling protein and said other cell signaling protein are both in a dephosphorylated state, said second pair state value being less than said first pair state value; and

- c) assigning a third pair state value when said one cell signaling protein and said other cell signaling protein are in different phosphorylation states, said third pair state value being less than said second pair state value.

5     20.     The method of claim 17 wherein identifying cell signaling protein pairs comprises identifying each cell signaling protein pair having a coregulation coefficient greater than a threshold coregulation value.

10     21.     The method of claim 20 wherein identifying cell signaling protein pairs further comprises producing a list of coregulated cell signaling protein pairs, said list comprising an identification of each said cell signaling protein pair having a coregulation coefficient greater than said threshold coregulation value.

15     22.     The method of claim 21 wherein identifying cell signaling protein pairs further comprises producing a list of clusters of coregulated cell signaling protein pairs, each said cluster comprising a group of said coregulated cell signaling protein pairs for which each member of each pair is present in at least one other pair of said group.

20     23.     The method of claim 1 wherein producing a comparison value comprises producing a linkage coefficient for each pair of said cell signaling proteins, as a function of a coexpression coefficient representing a degree of coexpression of one cell signaling protein of said pair and the other cell signaling protein of said pair, and of a coregulation coefficient representing a degree of coregulation of said one cell signaling protein of said pair and said other cell signaling protein of said pair, each said linkage coefficient representing a degree of association between said one cell signaling protein and said other cell signaling protein.

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24. The method of claim 23 wherein producing said linkage coefficient comprises, for each said pair, dividing said coregulation coefficient by said coexpression coefficient.
- 5 25. The method of claim 24 further comprising producing a list of linked cell signaling protein pairs, said list comprising an identification of each said cell signaling protein pair having a linkage coefficient greater than or equal to a threshold linkage value.
- 10 26. The method of claim 24 further comprising associating at least some of said cell signaling proteins with respective common signaling pathways, in response to said linkage coefficients.
- 15 27. The method of claim 26 wherein associating comprises identifying a group of said cell signaling proteins for which each said linkage coefficient linking each cell signaling protein to each other cell signaling protein of said group is greater than or equal to a threshold linkage value.
- 20 28. The method of claim 27 wherein identifying said group comprises:
- a) generating a linkage list comprising a first cell signaling protein;
  - b) adding, to said linkage list, each other said cell signaling protein for which said linkage coefficient for said first cell signaling protein and said other cell signaling protein is greater than or equal to said threshold linkage value; and
  - c) eliminating, from said linkage list, each cell signaling protein on said linkage list for which said linkage coefficient for said each cell signaling protein and at least one other cell signaling protein on said linkage list is less than said threshold linkage value.
- 25 29. The method of claim 27 further comprising producing lists of said common signaling pathways.

30. The method of claim 1 further comprising producing said data values representing said physical properties of said respective cell signaling proteins.
- 5 31. The method of claim 30 wherein producing said data values comprises producing signals representative of proteins in a single dimension in an electrophoresis gel.
32. The method of claim 31 further comprising producing said electrophoresis gel.
- 10 33. An apparatus for identifying associated cell signaling proteins, the apparatus comprising:
- a) a receiver operable to receive data values representing physical properties of respective cell signaling proteins; and
  - b) a processor circuit in communication with said receiver, said processor circuit being configured to:
    - 15 i) produce and store, in a memory, a comparison value for each pair of said cell signaling proteins in response to said data values; and
    - 20 ii) identify cell signaling protein pairs having comparison values satisfying a condition indicative of an association between the cell signaling proteins.
34. The apparatus of claim 33 further comprising said memory.
35. The apparatus of claim 34 wherein said memory comprises a random access memory.
- 25 36. The apparatus of claim 33 wherein said processor circuit is configured to normalize said data values relative to at least one reference value, prior to producing said comparison values.

37. The apparatus of claim 33 wherein said processor circuit is configured to produce a list of pairs of associated cell signaling proteins.
38. The apparatus of claim 33 wherein said processor circuit is configured to produce a list of clusters of associated cell signaling proteins.
- 5 39. The apparatus of claim 37 wherein said processor circuit is configured to identify a cluster of associated cell signaling proteins, said cluster comprising a group of said pairs of associated cell signaling proteins for which each member of each said pair is present in at least one other pair of said group.
- 10 40. The apparatus of claim 39 wherein said processor circuit is configured to identify said cluster of associated cell signaling proteins, by:
- a) generating a cluster list associated with a first cell signaling protein pair, said cluster list comprising an identification of said first cell signaling protein pair;
  - 15 b) adding, to said cluster list, an identification of each of said pairs that includes at least one cell signaling protein already present in said cluster list;
  - c) repeating said adding following each said adding of pairs to said cluster list, to effectively add to said cluster list each of said pairs that includes at least one cell signaling protein present in at least  
20 one pair added to said cluster list;
  - d) eliminating, from said cluster list, each of said pairs that includes at least one cell signaling protein not found in at least one other pair in said cluster list; and
  - 25 e) repeating said eliminating following each said eliminating of pairs, to effectively eliminate from said cluster list each of said

pairs that includes at least one cell signaling protein not present in at least one other non-eliminated pair in said cluster list.

- 5      **41.** The apparatus of claim **33** wherein said receiver is operable to receive, sets of cell signaling protein data, each set comprising said data values, said data values representing amounts of respective corresponding cell signaling proteins in biological material corresponding to said set.
- 10      **42.** The apparatus of claim **41** wherein said processor circuit is configured to produce, as said comparison values, a coexpression coefficient for each pair of said cell signaling proteins, each said coexpression coefficient representing a degree of coexpression of one cell signaling protein of said pair and the other cell signaling protein of said pair.
- 15      **43.** The apparatus of claim **42** wherein said processor circuit is configured to produce each said coexpression coefficient by:
- a) for each set, calculating a difference value equal to an absolute value of a difference between said data value corresponding to said one cell signaling protein and said data value corresponding to said other cell signaling protein; and
  - b) adding said difference values for each of said sets to produce a sum of difference values.
- 20      **44.** The apparatus of claim **43** wherein said processor circuit is configured to divide said sum by the number of said sets to produce said coexpression coefficient corresponding to said one cell signaling protein and said other cell signaling protein.
- 25      **45.** The apparatus of claim **43** wherein said processor circuit is configured to identify said cell signaling protein pairs by identifying each cell signaling protein pair having a coexpression coefficient less than or equal to a threshold coexpression value.

- 5      46.    The apparatus of claim 43 wherein said processor circuit is configured to produce a list of coexpressed cell signaling protein pairs, said list comprising an identification of each said cell signaling protein pair having a coexpression coefficient less than or equal to said threshold coexpression value.
- 10      47.    The apparatus of claim 46 wherein said processor circuit is configured to produce a list of clusters of coexpressed cell signaling protein pairs, each said cluster comprising a group of said pairs of coexpressed cell signaling proteins for which each member of each pair is present in at least one other pair of said group.
- 15      48.    The apparatus of claim 33 wherein said receiver is operable to receive sets of cell signaling protein data, each set comprising said data values, said data values indicating phosphorylation states of respective cell signaling proteins in biological material corresponding to said set.
- 20      49.    The apparatus of claim 48 wherein said processor circuit is configured to produce, as said comparison values, a coregulation coefficient for each pair of said cell signaling proteins, each said coregulation coefficient representing a degree of coregulation of one cell signaling protein of said pair and the other cell signaling protein of said pair.
- 25      50.    The apparatus of claim 49 wherein said processor circuit is configured to produce each said coregulation coefficient by:
- a)    for each set, assigning a pair state value as a function of phosphorylation states of said one cell signaling protein and said other cell signaling protein; and
  - b)    adding said pair state values for each of said sets to produce a sum of pair state values.
51.    The apparatus of claim 50 wherein said processor circuit is configured to divide said sum by the number of said sets to produce said

coregulation coefficient corresponding to said one cell signaling protein and said other cell signaling protein.

52. The apparatus of claim **50** wherein wherein said processor circuit is configured to assign said pair state value by:

- 5 a) assigning a first pair state value when said one cell signaling protein and said other cell signaling protein are both in a phosphorylated state;
- 10 b) assigning a second pair state value when said one cell signaling protein and said other cell signaling protein are both in a dephosphorylated state, said second pair state value being less than said first pair state value; and
- 15 c) assigning a third pair state value when said one cell signaling protein and said other cell signaling protein are in different phosphorylation states, said third pair state value being less than said second pair state value.

53. The apparatus of claim **50** wherein said processor circuit is configured to identify said cell signaling protein pairs by identifying each cell signaling protein pair having a coregulation coefficient greater than a threshold coregulation value.

20 54. The apparatus of claim **53** wherein said processor circuit is configured to produce a list of coregulated cell signaling protein pairs, said list comprising an identification of each said cell signaling protein pair having a coregulation coefficient greater than said threshold coregulation value.

25 55. The apparatus of claim **54** wherein said processor circuit is configured to produce a list of clusters of coregulated cell signaling protein pairs, each said cluster comprising a group of said coregulated cell signaling

protein pairs for which each member of each pair is present in at least one other pair of said group.

- 5 56. The apparatus of claim 33 wherein said processor circuit is configured to produce, as said comparison values, a linkage coefficient for each pair of said cell signaling proteins, as a function of a coexpression coefficient representing a degree of coexpression of one cell signaling protein of said pair and the other cell signaling protein of said pair, and
- 10 of a coregulation coefficient representing a degree of coregulation of said one cell signaling protein of said pair and said other cell signaling protein of said pair, each said linkage coefficient representing a degree of association between said one cell signaling protein and said other cell signaling protein.
- 15 57. The apparatus of claim 56 wherein said processor circuit is configured to produce each said linkage coefficient by, for each said pair, dividing said coregulation coefficient by said coexpression coefficient.
- 20 58. The apparatus of claim 57 wherein said processor circuit is configured to produce a list of linked cell signaling protein pairs, said list comprising an identification of each said cell signaling protein pair having a linkage coefficient greater than or equal to a threshold linkage value.
- 25 59. The apparatus of claim 57 wherein said processor circuit is configured to associate at least some of said cell signaling proteins with respective common signaling pathways, in response to said linkage coefficients.
60. The apparatus of claim 59 wherein said processor circuit is configured to associate said cell signaling proteins with said pathways by identifying a group of said cell signaling proteins for which each said linkage coefficient linking each cell signaling protein to each other cell signaling protein of said group is greater than or equal to a threshold linkage value.

61. The apparatus of claim 60 wherein said processor circuit is configured to identify said group by:

- a) generating a linkage list comprising a first cell signaling protein;
- b) adding, to said linkage list, each other said cell signaling protein for which said linkage coefficient for said first cell signaling protein and said other cell signaling protein is greater than or equal to said threshold linkage value; and
- c) eliminating, from said linkage list, each cell signaling protein on said linkage list for which said linkage coefficient for said each cell signaling protein and at least one other cell signaling protein on said linkage list is less than said threshold linkage value.

62. The apparatus of claim 60 wherein said processor circuit is configured to produce lists of said common signaling pathways.

63. The apparatus of claim 33 further comprising a measuring device operable to produce said data values representing said physical properties of said respective cell signaling proteins.

64. The apparatus of claim 63 wherein said measuring device comprises a chemiluminescence imager operable to produce signals representative of proteins in a single dimension in an electrophoresis gel.

65. The apparatus of claim 64 wherein said measuring device further comprises an electrophoresis apparatus operable to produce said electrophoresis gel.

66. The apparatus of claim 65 wherein said electrophoresis apparatus comprises a one-dimensional sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) measuring system.

67. An apparatus for identifying associated cell signaling proteins, the apparatus comprising:

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- a) means for receiving data values representing physical properties of respective cell signaling proteins;
  - b) means for producing and for storing a comparison value for each pair of said cell signaling proteins in response to said data values; and
  - c) means for identifying cell signaling protein pairs having comparison values satisfying a condition indicative of an association between the cell signaling proteins.
- 10 68. An apparatus for identifying associated cell signaling proteins, the apparatus comprising:
- a) means for receiving data values representing physical properties of respective cell signaling proteins;
  - b) means for producing a comparison value for each pair of said cell signaling proteins in response to said data values;
  - 15 c) means for storing said comparison values, said means for storing comprising a random access memory; and
  - d) means for identifying cell signaling protein pairs having comparison values satisfying a condition indicative of an association between the cell signaling proteins.
- 20 69. A computer readable medium for providing instructions for directing a programmable device to:
- a) receive data values representing physical properties of respective cell signaling proteins;
  - b) produce and store a comparison value for each pair of said cell signaling proteins in response to said data values; and
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- c) identify cell signaling protein pairs having comparison values satisfying a condition indicative of an association between the cell signaling proteins.

70. A computer data signal embodied in a carrier wave comprising:

- 5           a) a first code segment for directing a programmable device to receive data values representing physical properties of respective cell signaling proteins;
- b) a second code segment for directing said programmable device to produce and store a comparison value for each pair of said  
10           cell signaling proteins in response to said data values; and
- c) a third code segment for directing said programmable device to identify cell signaling protein pairs having comparison values satisfying a condition indicative of an association between the cell signaling proteins.